Daclatasvir (Daklinza™) and Sofosbuvir (Sovaldi™) for Genotype 3 Patients

Criteria for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive daclatasvir and sofosbuvir-based regimen without local adjudication.*

☐ Limited Life Expectancy (refer to issues for consideration)

☐ Patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis (due to sofosbuvir)

☐ Patients who have virologically failed prior treatment with a NS5A inhibitor based regimen (i.e. ledipasvir, ombitasvir, or daclatasvir) unless resistance testing indicates susceptibility to daclatasvir

☐ Documented ongoing nonadherence to prescribed medications or medical treatment, failure to complete hepatitis C virus (HCV) disease evaluation appointments and procedures or unable to commit to scheduled follow-up/monitoring for the duration of treatment

☐ HCV **Genotype 1, 2, 4, 5, and 6** infection

☐ HCV **Genotype 3 without cirrhosis** (Refer to ledipasvir/sofosbuvir CFU for treatment options for non-cirrhotics)

☐ Known hypersensitivity to any component of the planned treatment regimen

☐ Co-administration with strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, or St. John's wort (i.e. contraindications in the prescribing information)

☐ Co-administration with moderate inducers of CYP3A, including bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcilin, rifapentine (consideration should be made in altering interacting medication rather than using 90mg of daclatasvir due to high cost).

☐ Co-administration of amiodarone (refer to Issues for Consideration)

When daclatasvir and sofosbuvir regimen is used in combination with ribavirin

☐ Any contraindications and/or intolerance to ribavirin

Contraindication and/or intolerance to ribavirin: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e. symptomatic or baseline hemoglobin <10g/dL) and/or history of *significant* adverse events with previous ribavirin-containing regimen. **Please note that history of anemia related to ribavirin-containing regimen should be evaluated in context of PBM CFU for ESA (i.e., ribavirin dose reduction to 600mg must have been instituted prior to consideration of ESA use) and does not necessarily constitute intolerance.

Inclusion Criteria *The answers to ALL OF THE FOLLOWING must be fulfilled in order to meet criteria.*

☐ Under care of and/or in collaboration with an experienced VA HCV practitioner

☐ Adherence counseling performed including laboratory follow-up and documented understanding by patient

☐ **HCV Genotype 3 with cirrhosis** (Refer to ledipasvir/sofosbuvir CFU for treatment options for non-cirrhotics)

☐ Treatment regimen and duration based upon patient characteristics according to the dosage and administration section below

For women of childbearing potential receiving ribavirin or who have a male partner receiving ribavirin:

☐ When daclatasvir and sofosbuvir is used in combination with ribavirin therapy (which is pregnancy category X), the ribavirin should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with daclatasvir and sofosbuvir with concomitant ribavirin, and for 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time.

Dosage, Administration

Treatment regimen and duration are based upon patient characteristics as described in the Table below**. Refer to sofosbuvir and ledipasvir/sofosbuvir CFU for treatment options with ledipasvir/sofosbuvir in treatment-naïve and -experienced without cirrhosis as well as sofosbuvir/PEG/riba for treatment-experienced with or without cirrhosis.**

Daclatasvir and Sofosbuvir

Daclatasvir 60mg orally once daily and sofosbuvir 400mg orally once daily with or without food in combination with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day)

Note:
If co-administered with strong CYP3A inhibitors, reduce daclatasvir to 30mg once daily
If co-administered with moderate CFY3A inducers, increase daclatasvir to 90mg once daily

Population includes patients with HCV monoinfected, HCV/HIV-1 co-infected, or hepatocellular carcinoma (HCC)[a]	Dosage Regimens	Total treatment duration
HCV Genotype 3[b]		
Treatment-naïve without cirrhosis	Refer to Ledipasvir/sofosbuvir CFU	-------
Treatment-naïve with compensated cirrhosis	Daclatasvir and Sofosbuvir plus ribavirin OR Sofosbuvir plus peginterferon and ribavirin	16 weeks OR 12 weeks
Treatment-naïve with decompensated cirrhosis	Daclatasvir and Sofosbuvir plus ribavirin (initiate ribavirin at 600mg/day and titrate up as tolerated)	24 weeks
Treatment-experienced (PEG/riba only) without cirrhosis	Refer to Ledipasvir/sofosbuvir CFU	-------
Treatment-experienced[c] with compensated cirrhosis	Daclatasvir and Sofosbuvir plus ribavirin OR Sofosbuvir plus peginterferon and ribavirin	16 weeks OR 12 weeks
Treatment-experienced[c] with decompensated cirrhosis	Daclatasvir and Sofosbuvir plus ribavirin (initiate ribavirin at 600mg/day and titrate up as tolerated)	24 weeks

[a]Refer to Issues for Consideration for alternative treatment options including patients pre- and post-transplant.
[b]Refer to Issues for Consideration for additional information.
[c]In clinical trials, treatment-experienced was defined as previous peginterferon/ribavirin therapy or sofosbuvir/ribavirin therapy

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving HCV therapy, the following monitoring is recommended:

- **Hematologic adverse events (anemia) if co-administered with ribavirin:** Complete blood count with white blood cell differential counts should be obtained at baseline and at treatment weeks 2, 4, 8, and 12, and at other time points, as clinically appropriate. Initial management of anemia should consist of ribavirin dose reduction for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- Virologic monitoring **should be assessed to determine response to treatment. Patients should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.**
- **Sustained Viral Response (SVR) or non-response** should be determined by measurement of HCV RNA 12 weeks after stopping treatment.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.
- **Monthly pregnancy tests** for women of childbearing potential receiving ribavirin

Issues for Consideration

Treatment Considerations:

- Refer to separate PBM CFU for sofosbuvir and ledipasvir/sofosbuvir for other Genotype 3 therapeutic options. Also, refer to OPH HCV Treatment Considerations for more details regarding clinical data.
- **In genotype 3 patients** with compensated cirrhosis, available data indicate that DCV+SOF+RBV for 16 weeks provides an SVR rate of >90%. In the ALLY-3 Plus study 21/24 (6/6 with advanced fibrosis and 15/18 with cirrhosis) patients receiving 12 weeks of DCV+SOF+RBV achieved an SVR-4 whereas 25/26 (8/8 with advanced fibrosis and 17/18 with cirrhosis) patients receiving 16 weeks of DCV+SOF+RBV achieved an SVR-4. Other data indicate that twelve week regimens of DCV+SOF+RBV or DCV+SOF in GT3 patients with cirrhosis (including decompensated cirrhotics) were lower and ranged from 70% (80/114) to 83% (5/6) for those receiving DCV+SOF+RBV and 58% (11/19), 69% (9/13) and 71% (5/7) in those receiving DCV+SOF. SVR rates in GT3 cirrhotic patients treated in real-world settings with LDV/SOF+RBV were 59% (36/61). Compassionate use programs comparing 12 and 24 week regimens have reported higher SVRs with 24 week regimens. In a mostly treatment experienced, cirrhotic population receiving DCV+SOF for 12 or 24 weeks, interim SVR12 rates were 82% (23/28) and 93% (39/42), respectively. In the same population, those who received DCV+SOF+RBV for 12 or 24 weeks, interim SVR12 rates were 100% (3/3) and 93% (13/14). In another smaller population of cirrhotics, interim SVR12 rates achieved with DCV+SOF were 100% in patients treated for 12 (3/3) or 24 (7/7) weeks; interim SVR12 rates achieved with DCV+SOF+RBV for 12 or 24 weeks were 75% (3/4) and 88% (7/8).
- **If a patient cannot tolerate ribavirin**, then DCV + SOF alone can be considered for the remainder of therapy. These recommendations should be interpreted with caution because much of the data are available only from abstracts, non-randomized preliminary studies (e.g., SVR 4 data), and sub-analyses with small sample sizes.
- **In genotype 2 patients who cannot tolerate ribavirin,** AASLD recommends DCV+SOF as an alternative to SOF+RBV in patients who cannot tolerate RBV (see description of contraindications and intolerance to RBV under exclusion criteria). Local adjudication should be utilized for this use of DCV+SOF.
- **Resistance Testing:** Baseline testing for NS5A RAVs is recommended to determine treatment options for all cirrhotic GT3 patients regardless of prior treatment as well as in treatment-experienced patients who have received any regimen (this includes patients who previously received only PEG/riba). If the Y93H RAV is present, the patient should be informed of the potential for a lower chance of SVR. Consult a practitioner with expertise to weigh the risks versus benefits of treatment. Strong consideration should be given to testing for NS5B resistance in patients who have previously been treated with a sofosbuvir containing regimen.
- **Populations Unlikely to Benefit from HCV Treatment:** According to AASLD/IDSA HCV Guidelines, "patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. Chronic hepatitis C is associated with a wide range of comorbid conditions. Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence."
- **Chronic HCV-infected patients with minimal fibrosis** (METAVIR stage 0 or 1 based on an adequate liver biopsy specimen) and no other risk factors for liver disease are at lower risk for developing advanced liver disease in the short-term. After a thorough discussion of prognosis and treatment options, the provider and patient may agree to observation and defer treatment. Treatment should be reconsidered if liver disease progresses. Modifiable risk factors for progression of liver disease, such as alcohol use, should be addressed.

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV:** Co-infected patients should be managed in consultation with an experienced HIV provider. Refer to PI for potential dosage modifications and/or additional monitoring for adverse events when co-administered with certain antiretrovirals.
- **Treatment Experienced GT3 (Prior DAA-based therapy):** The optimal DAA regimen for treatment-experienced patients particularly those patients with cirrhosis are uncertain. The following recommendations are based on expert opinion. It is likely that patients who fail treatment with an NS5A inhibitor will have NS5A resistant associated variants that will confer resistance to all other, currently-available NS5A inhibitors. Therefore, baseline testing for NS5A RAVs is recommended for GT3 treatment-experienced and/or cirrhotic patients to determine treatment options. If the Y93H RAV is present, the patient should be informed of the potential for a lower chance of SVR. Consult a practitioner with expertise to weigh the risks versus benefits of treatment.
- **Decompensated cirrhosis:** Data supporting daclatasvir+sofosbuvir+ribavirin use in GT3 decompensated cirrhotics are available from two open-label non-randomized early access programs. In the French Multicenter Compassionate Use Program, 601 patients received DCV +SOF for 12 or 24 weeks with RBV added at the provider's discretion; 17% were HIV co-infected, 73% were treatment experienced and 77% were cirrhotic of which 70%, 9% and 3% had a Child-Pugh score of A, B or C, respectively. 20% of patients received RBV and 93% of patients received treatment for 24 weeks. In cirrhotics receiving DCV+SOF for 12 or 24 weeks, interim SVR12 rates were 82% (23/28) and 93% (39/42), respectively. In cirrhotics who received DCV+SOF+RBV for 12 or 24 weeks, interim SVR12 rates were 100% (3/3) and 93% (13/14), respectively. In the UK Early Access Program, GT3 patients with decompensated cirrhosis received 12 weeks of treatment with either DCV+SOF ± RBV (n=114) or LDV/SOF± RBV (n=61) as decided by the provider; 94% had current or previous decompensated cirrhosis (CPT B 66%, CPT C 10%, mean MELD score 11.6). SVR rates were 70% (80/114) for DCV+SOF+RBV, 71% (5/7) for DCV+SOF and 59% (36/61) for LDV/SOF+RBV, Due to safety concerns, patients with decompensated liver disease should not receive a regimen containing peginterferon and/or a NS3-4A protease inhibitor. **Treatment of patients with decompensated cirrhosis should be managed by physicians with extensive experience in the treatment of patients with advanced liver disease**
- **Hepatocellular Carcinoma (HCC) or other cancer:** It is reasonable to treat HCV in any patient with HCC, history HCC, or other malignancy *if there is a high likelihood that the cancer has been cured*. Curative treatments for solitary or early stage HCCs within Milan criteria include resection and thermal ablation as well as liver transplantation (TACE, radioembolization, radiation therapy and targeted/chemotherapy are NOT considered curative). For those receiving resection or thermal ablation, if staging studies indicate good likelihood of success (absence of macrovascular invasion, clear margins, etc.) and if follow-up restaging studies show no

evidence of cancer recurrence, then treatment of HCV may be offered.

- **Hepatic Impairment:**
  - Daclatasvir: No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
  - Sofosbuvir: No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
- **Pre-liver transplant (also see decompensated cirrhosis and HCC bullet above): The decision to treat *any* patient awaiting transplantation should be made in consultation with the transplant center where the patient is listed and determined on a case by case basis**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (pre- or post-) or whether treatment is appropriate given patient's prognosis.
- **Post-liver transplant: Any daclatasvir and sofosbuvir-based regimen should only be used in patients who are being actively managed by physicians with extensive experience in the treatment of post-transplant patients**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation.
- **Renal Impairment:**
  - Daclatasvir: No dosage adjustment is necessary for patients with any degree of renal impairment.
  - Sofosbuvir: No dosage adjustment is necessary for patients receiving sofosbuvir with mild or moderate renal impairment; sofosbuvir was not studied in patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis. The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min/1.73m^2.
- **Substance or Alcohol Use:** All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C . Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and is strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation.
- **Mental Health Conditions:** HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.
- **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information states that no dosage adjustments are needed for sofosbuvir or daclatasvir for patients receiving tenofovir.

Drug-interactions:

- Consult both prescribing information prior to use of daclatasvir and sofosbuvir-based regimen for potential drug interactions
  - Sofosbuvir is substrates of drug transporter P-gp and breast cancer resistance protein (BCRP); drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations.
  - Daclatasvir is a substrate of CYP3A; moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of daclatasvir while strong inhibitors of CYP3A may increase plasma levels of daclatasvir.
  - Daclatasvir is an inhibitor of P-glycoprotein transporter (P-gp), organic anion transporting polypeptide (OATP) 1B1 and 1B3, and breast cancer resistance protein (BCRP). Administration of daclatasvir may increase systemic exposure to medications that are substrates of P-gp, OATP 1B1 or 1B3, or BCRP.
- **Bradycardia with amiodarone coadministration:** Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with SOF with daclatasvir is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Refer to PI for more details.

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use and limiting acetaminophen use to 2g/day.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov

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